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CARDIOPULMONARY RESPONSES TO HYPOTHERMIA AND CERTAIN OTHER ENVIRONMENTAL STRESSES

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Contract Monitor: Donald A. Rosenbaum
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[Prepared under Contract No. AF 33(616)-6803
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FOREWORD

These studies were initiated by the Biomedical Laboratory, Wright-Patterson Air Force Base, Ohio. The research was conducted by Duke University, Durham, North Carolina, under contract No. AF 33 (616)-6803. Professor F. G. Hall was the principal investigator for Duke University. Donald A. Rosenbaum, Respiration Section, Physiology Branch, Biomedical Laboratory, served as contract monitor for the 6570th Aerospace Medical Research Laboratories. The work was performed in support of Project No 7163, "Physiology Research," Task No. 716301. The research sponsored in this contract was started in September 1960 and was completed in October 1962.

The experiments reported herein were conducted according to the "Principles of Laboratory animal care" established by the National Society for Medical Research and the American Physiological Society.

ABSTRACT

Respiratory regulation was studied at normal and sub-normal body temperatures. Hypoxia and body temperature were found to operate reciprocally in determining utilization of oxygen in a closed environment. Respiratory and circulatory responses to imposed tracheal obstruction were studied in normothermic and hypothermic anesthetized animals. These responses were found to be related to the degree of hypoxia which developed rather than to body temperature, per se. Changes in anatomical and physiological dead space were also measured during reduction of body temperature. There were only small changes in respiratory dead space. No significant impairment of gas transport occurred at body temperatures as low as 28°C.

Reflex activity was also studied in normothermic and hypothermic animals. Hypothermic animals retain reflex activity but the magnitude of the responses is less than at normal body temperature. The augmented response to nor-epinephrine was greater than that for epinephrine during reduction in body temperature to 28°C. Vagal reflexes also operate at body temperatures as low as 28°C. It was found that animals respond to carbon dioxide stress essentially in the same manner in the hypothermic as in the normothermic state but at a lower order of magnitude.

PUBLICATION REVIEW

This technical documentary report has been reviewed and is approved.

Jos M Quashnock

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INTRODUCTION

Knowledge of the effects of environmental stresses upon man and animals is essential to progress in space exploration as well as in certain fields of medical research. Living things on this earth are adapted to the environment on this earth. A living organism cannot be thought of as separate from its environment. While man and other forms of life seem to maintain a physiological and biochemical constancy within themselves (their internal environment), the regulation of these processes which maintain this constancy is stimulated by changes or stresses imposed by the external environment. Consequently, no animal is ever free, unaffected, or independent of the external environment. This is a concept to be shared by both biologist and engineer. If man and animals are to be sent to regions distant from this earth, an intimate environment similar to that on this earth must always accompany them.

There is a great body of information about the characteristics of the physical environment of organisms. There are, however, many gaps in knowledge of how animals respond to changes in environment and how they adjust to these changes. More quantitative information is needed to explain the interaction of physiological processes in the regulation of homoestasis within the animal body following exposure to adverse stresses from without. Each of the investigations reported herein has been an attempt to add new information as to the manner in which an organism adjusts its internal regulatory processes to changes in its external environment.

SECTION I

PHYSIOLOGIC FACTORS WHICH LIMIT THE MINIMAL UTILIZABLE OXYGEN IN A MICROENVIRONMENT

In the studies reported here numerous experiments have been performed on albino rats in a closed environment and measurements have been made to determine the minimal level at which utilizable oxygen can be removed from the environment. This is called the critical oxygen tension. Several physiologic factors which influence the critical oxygen tension were studied. The problem of critical oxygen tension is only one aspect of the broader one of hypoxia tolerance.

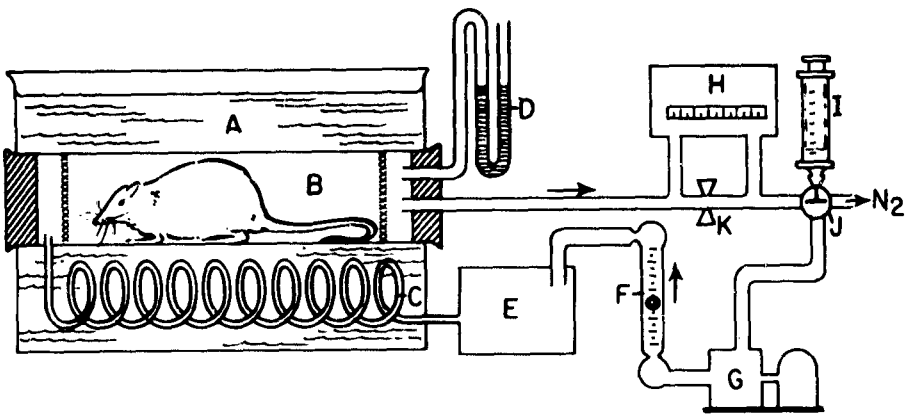
There are many physiologic factors which affect tolerance to hypoxia. Certainly blood plays one of the most important roles since it is the only means of transport between the gases in the lungs and the cellular sites of utilization. The ability of the blood to carry on this transport function depends upon several factors: the alveolar tension of oxygen, affinity of its hemoglobin for oxygen, the amount of hemoglobin available for transport, the circulation time of the blood, and the tissue capillary density. Adolph (1) pointed out that adjustments to various physical factors in the environment overlap.

It is generally accepted that the affinity of hemoglobin for oxygen is a major factor in determining tolerance to hypoxia. It has also been stated as a corollary that an increased oxygen affinity enables animals to obtain oxygen at lower oxygen tensions. Barker (2) stated that maximal increases in tolerance are achieved only under optimal conditions of oxygen tension duration. This author also found no significant effect upon tolerance to hypoxia due to alterations of total oxygen capacity. Such tests of tolerance to hypoxia in animals have usually been observations of reflex activity, or measurements of survival time.

In the studies reported here, animals were placed in a closed microenvironment and the oxygen tension of this environment decreased directly as a consequence of the utilization of oxygen by the animal. The tension at which no further lowering occurred was taken as the critical level.

PROCEDURE

Apparatus. The apparatus shown in Figure 1 consisted of a plastic tube, B, 1200 ml. capacity, inserted through the sides of a water bath, A. This tube was closed at each end by large rubber stoppers. Water bath, A, was temperature regulated to within 0.1° C. A manometer containing water, D, was used to indicate changes in pressure in chamber B. Atmospheric pressures



A - Water Bath
B - Metabolism Chamber
C - Copper Coil
D - Manometer
E - CO_2 Absorber
F - Flowmeter
G - Dynapump
H - Pauling Meter
I - 100 ml. Syringe
J - 3 Way Petcock
K - Flow Regulator

FIG. 1. Schematic diagram of apparatus used to determine critical oxygen tension of animals.

were maintained during each experiment. Air was circulated throughout the system by a dynapump, G. Flowmeter, F, indicated the flow which was maintained at eight liters per minute. Pauling Oxygen meter, H, was used to indicate partial pressure of oxygen within the closed system. By-pass regulator, K, was used to maintain a constant flow through the Pauling meter and to permit a larger flow throughout the system. Air from the dynapump was circulated through vessel, E, which contained Baralyme for the absorption of CO_2 and thence through copper coil, C, to bring the temperature of the circulating air to bath temperature. Analyses of the circulated air showed that no measurable CO_2 was recirculated. Between the Pauling meter and the dynapump a by-pass was arranged which permitted the addition of N_2 to the circulating air. This was admitted to the system by 100 ml. syringes, I, which in turn were filled from a cylinder containing nitrogen. Nitrogen was admitted in amounts to maintain pressure in the system equal to atmospheric pressures as indicated on manometer, D. A record of nitrogen added was kept which was used in calculating the oxygen consumption of the experimental animal. The total capacity of the system (without the rat) was 2012 ml.

The method for equilibration of blood with various gas mixtures and the determination of gas content of blood has been described by Hall (9).

Experimental Animals. Rats weighing approximately 300 grams were used. These were from the colonies raised in the Duke University Animal Department under carefully controlled conditions. Rats were tested separately by the following procedure. A small thermocouple was inserted 2 inches within the rectum and the leads carried to a galvanometer which would indicate temperatures to $\pm$ 0.01° C. Temperature readings were recorded every minute. Chamber B was darkened to prevent extraneous stimuli from exciting animals during experiments. Recordings of oxygen tension within the system were made at one or two minute intervals. Records were kept of the volume of nitrogen gas added to maintain atmospheric pressures within the system. Animals were autopsied for gross pathological changes. None were observed in the results reported and all rats were regarded as being within the normal physiologic range.

RESULTS AND DISCUSSION

Two physiologic factors act reciprocally to influence utilization of oxygen in animals in a closed environment. These are body temperature and oxygen tension of tissues. Both factors are related directly to conditions in the external environment. The interdependence of these two factors is illustrated in Figures 2 and 3.

The Effect of Hypoxia on Body Temperature. As the organism becomes hypoxic in a closed environment, thermal regulatory mechanisms begin to fail. It will be noted in Figure 2, when rats were kept at 10° C, and became hypoxic, that body temperature fell 9° C. below the normal level. In control

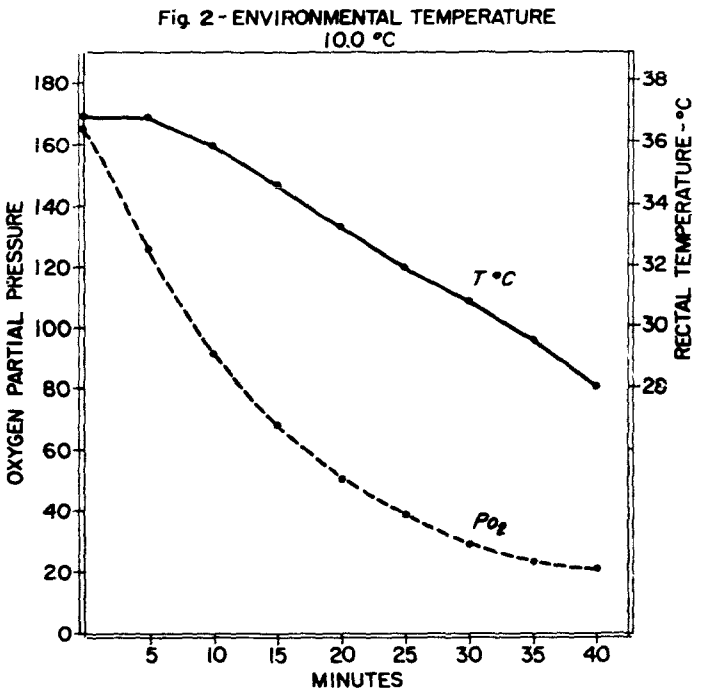


FIG. 2. Graphs showing the utilization of oxygen from a closed environment of 10°C. and concomitant changes in body temperature with time.

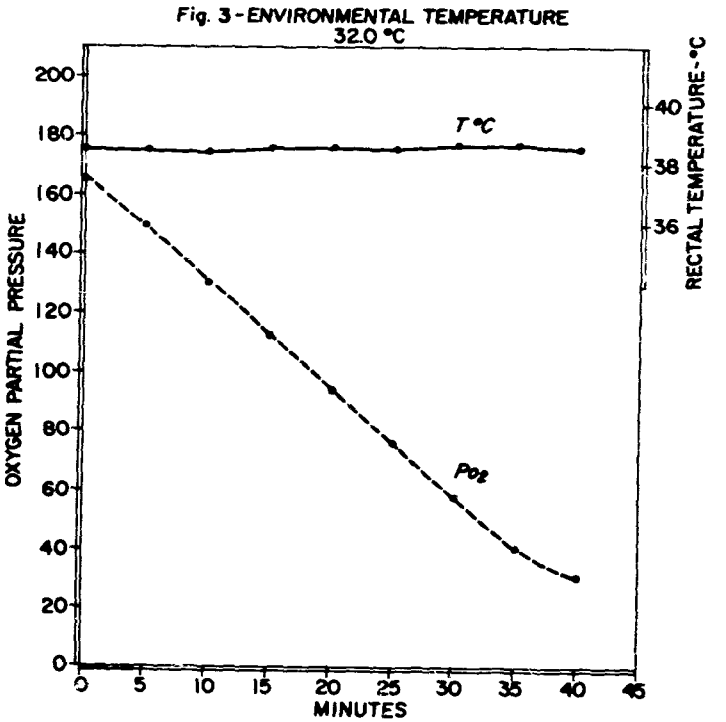


FIG. 3. Graph showing the utilization of oxygen from a closed environment of 32°C. and concomitant changes in body temperature with time.

experiments conducted in the same apparatus and kept at 10° C. but with oxygen tensions of the environment maintained at 160mm. Hg., body temperatures fell only 2°-3° C. for the same time intervals as in the hypoxic experiments. It should be stated that in all of these experiments air was circulated past experimental animals at eight liters per minute.

The Effect of Temperature on the Utilization of Oxygen in a Closed Environment. When the temperature falls below a critical level, oxygen consumption falls, and as the animal becomes more and more hypoxic the temperature regulatory mechanism becomes less effective. As a consequence of this, the slope of the curve of oxygen pressure within the environment curves more asymptotically with time until the critical oxygen pressure is reached, Figure 2. If on the other hand the temperature of the environment is kept at a level where the temperature regulatory mechanisms are not called upon to maintain body temperature by physiological responses, oxygen consumption proceeds at a more even rate. This is shown in Figure 3 and it will be noted that the slope of this curve is nearly linear until the critical oxygen tension is reached. The temperature of the environment in a closed system at which body temperature remains nearly constant is between 32° and 33° C. In Figure 2 it will be observed that rectal temperature of rats fell gradually with time when the environment was kept at 10° C. On the other hand when the environmental temperature was maintained at 32° C. rectal temperature changed only slightly with time. When rats were subjected to environmental temperatures above 33° C. the temperature regulatory mechanisms also became inadequate and body temperature rose with time. This also affects the critical oxygen tension level at which animals die. Alveolar vapor pressure of water decreases from 47 mm. Hg. at body temperature of 37° C. to 30 mm. Hg. at 29° C. This raises alveolar partial pressure of oxygen at the critical oxygen pressure less than 1 mm. Hg., which has little significance in these studies.

Table I shows the effects of temperature on the critical oxygen tension in 120 albino rats. Lower environmental temperatures decrease the tension at which animals can extract oxygen from the environment. Animals are more likely to survive at the lower temperature following exposures to low oxygen tensions. Ten rats exposed to 20 mm. Hg. oxygen tension and environmental temperatures of 10° C. were revived, while at environmental temperatures of 35° C. and at 34 mm. Hg. oxygen tension only six out of twenty revived.

Table II shows the effect of acclimatization on the critical oxygen tension. Acclimatization to hypoxia does not enable rats to extract oxygen from the environment at a lower tension. In this experiment 200 rats were used and they all appeared to withstand adequately the stress of acclimatization in a low pressure chamber. There were no weight losses and superficially all rats appeared normal. No gross pathology was observed on autopsy.

The question of the capacity of the microenvironment arose. Experiments were conducted on twelve rats in the same manner as described with the

TABLE I. Influence of environmental temperature on critical oxygen tension of normal albino rats.

Temp. °C.	Critical pO_2 mm. Hg.
10.0	22.8 ± 3.4 S.D.
20.0	27.0 ± 3.6
32.0	32.0 ± 4.0
35.0	34.1 ± 4.2
38.0	33.0 ± 5.0

TABLE II. Influence of acclimatization to hypoxia on critical oxygen tension of albino rats.

	Critical pO_2 mm. Hg.
Controls, (Bath temp. 35°C)	34.1 ± 4.2 S.D.
Acclimatized, (14 days at 380 mm. Hg.) (Bath temp. 35°C.)	34.6 ± 4.3
Controls, (Bath temp. 32°C.)	30.0 ± 4.0
Acclimatized, (40 days at 300 mm. Hg.) (Bath temp. 32°C.)	36.2 ± 4.4

exception that the capacity of the closed system was doubled. The critical oxygen pressures remained the same and no significant differences were observed.

Temperature has a marked effect upon the gas composition of blood. Figure 4 shows the gas composition of rat blood when equilibrated at tensions of 40 mm. Hg. CO_2 and 40 mm. Hg. O_2 at various temperatures ranging from 10° C. to 37.5° C. Figure 5 shows the oxygen dissociation curves of rat blood equilibrated at 40 mm. Hg. CO_2 and at various oxygen tensions. When rats reach the critical oxygen tension they are operating on the lower part of these curves. Tissues under these circumstances must be functioning at very low tensions of oxygen. The affinity of hemoglobin for oxygen is a major factor in enabling animals to obtain oxygen at lower oxygen tensions. The quality of the hemoglobin appears to be more important than the quantity or concentration of hemoglobin in the blood when the animal approaches the lethal level of oxygen supply.

One is led to the conclusion that critical oxygen tension results from the failure of the central respiratory centers to drive the ventilatory mechanisms of the respiratory system and not from failure of the heart or circulation. Tissues remove oxygen from the blood at very low tensions.

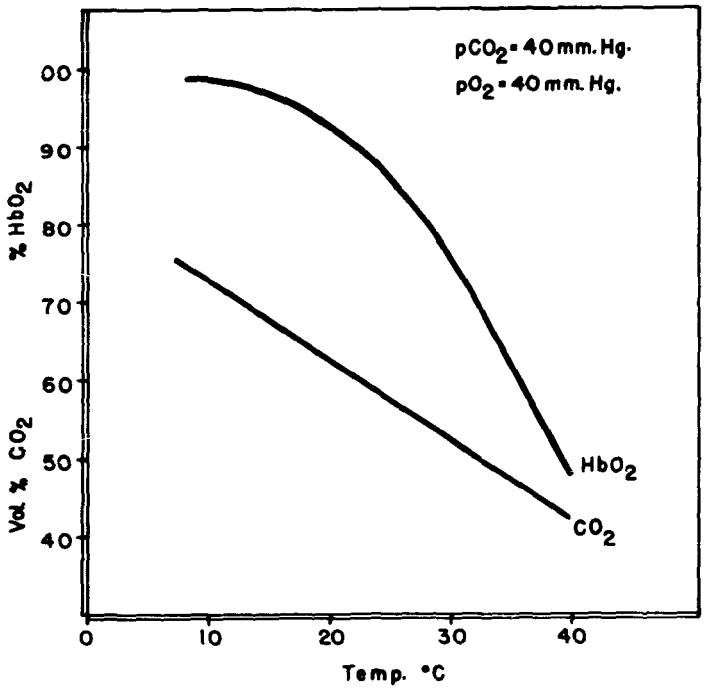


FIG. 4. Graphs showing $C0_2$ content and hemoglobin oxygen saturation on similar samples of rat blood at various temperatures and at 40 mm. Hg 0_2 and 40 mm. Hg $C0_2$.

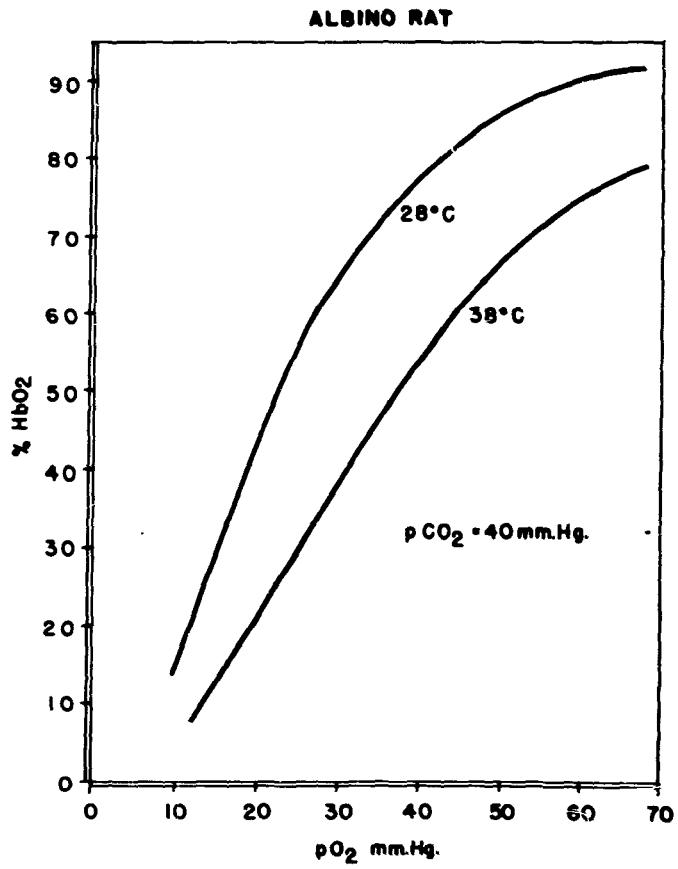


FIG. 5. Graphs showing the oxygen dissociation of hemoglobin at 28°C. and 37.5°C. at tensions of 40 mm. $C0_2$ for the albino rat.

SECTION II

EFFECT OF HYPOTHERMIA ON RESPONSES TO IMPOSED TRACHEA OBSTRUCTION

A necessary adjunct to a successful induction of hypothermic states for surgical procedures involves the application of methods to assure adequate alveolar ventilation of the patient. These methods frequently involve the use of respiratory apparatus and breathing valves which may lead to an increase in upper airway resistance. It has been shown by Hall and Zechman (6) that in anesthetized, normothermic dogs the primary effects of imposed resistance to tracheal air flow are a reduction of air flow velocity and an increase in the duration of the impeded phase. Concomitantly, pulmonary ventilation is reduced and alveolar carbon dioxide tension rises while there is a decrease in oxygen saturation. It was further shown that respiratory rate increased with increasing magnitudes of obstruction. However, if the animals were breathing 100% O_2 during obstruction, respiratory rates less than control were observed. It seemed then that the primary effect of breathing against airway resistances was a reduction in respiratory rate which could be masked if hypoxic conditions ensued. In view of the effects of reduction of temperature on blood gas tensions and the commensurate shift in the oxygen dissociation curve it was thought of value to study the effects of graded imposed tracheal obstruction in hypothermic animals and to compare the responses to those of the normothermic animal.

METHODS

Ten mongrel dogs ranging in weight from 14.6 to 24.1 kg (mean = 17.4 kg) were used in these experiments. Dial in urethan (Ciba), 55 mg/kg, was administered before surgical procedures and was not supplemented during the experiment. A specially constructed tracheal cannula, previously illustrated (6), into which various size plate orifices could be easily inserted was used. A monel wire-screen flowmeter was added to the tracheal cannula for recording respiratory flow patterns. Intratracheal pressures were recorded from a Statham pressure transducer attached to a side arm of the cannula. All respiratory parameters, namely, respiratory rate, tidal volume, pulmonary ventilation, maximum inspiratory and expiratory flow rates, and duration of inspiratory and expiratory phases of the cycle were calculated from the screen flow patterns. Maximum inspiratory and expiratory tracheal pressures were calculated from the recorded tracheal pressure patterns. Systemic arterial pressure and heart rate were recorded from a Statham transducer attached to a polyethylene catheter inserted into a femoral artery. Another catheter was inserted through a femoral vein into the right ventricle, verified from oscilloscope patterns of the pressure waves for withdrawing mixed venous blood.

Blood samples were withdrawn anaerobically from the arterial and venous catheters simultaneously. The samples were equilibrated tonometrically (9). Analyses were made of oxygen content, oxygen capacity, and carbon dioxide content by use of a Van Slyke manometric gas analyzer (29). Total hemoglobin was determined colorimetrically after converting hemoglobin in the samples to metcyanhemoglobin. The factor of 1.34 was used to calculate total hemoglobin oxygen capacity.

End-tidal carbon dioxide tension was measured with a Liston-Becker analyzer. All variables were recorded simultaneously on a Miller oscillograph. Recordings were made before and during the 11th-12th min after orifices of various sizes were inserted in the tracheal cannula.

Cardiac output was measured by use of the Fick principle. Expired gas was collected in a 100-liter plastic Douglas bag and the volume after collection measured with a dry-gas meter. Aliquot samples were collected and the oxygen tension determined, in duplicate, with a Pauling oxygen analyzer. The arterial-venous oxygen difference was calculated from the analyses of the arterial and mixed venous blood samples collected during the final minute of expired gas collection.

Three orifices were used, each being 1 mm in thickness with diameters of 1.9, 2.3, 3.2 mm, respectively. At least 15 min was allowed between the use of each orifice for recovery.

Following observations at normal body temperature the animals were immersed in an ice-water bath and cooled to 29 C. The animal was then removed from the water and the environmental temperature was adjusted to maintain the blood temperature between 27.5-28.5 C. The protocol used at 37 C was then repeated.

RESULTS

The salient features, with respect to the performance of hypothermic animals as compared to normothermic animals, in response to imposed tracheal resistance to air flow are shown in Figs. 6-8 and Tables 3 and 4. The figures were constructed so that points on the abscissa are shown as the reciprocals of the areas of the three orifices used, the minimal resistance of the respiratory apparatus is represented as control (C).

The influence of air flow resistance on respiratory rate and tidal volume is shown in Fig. 6 as per cent changes from the control values. At normal body temperature respiratory rate increased as the magnitude of the resistance was increased, so that at the highest resistance used the rate was 49% greater than that at control. When the blood temperature was reduced, an opposite response was noted, i.e., respiratory frequency decreased and tidal volume increased when tracheal resistance was added. However, at the highest level of resistance used the rate and depth of breathing approached control value.

Tracheal pressures and maximum air flow rates at the two body temperatures studied are shown in Fig. 7. The changes in tracheal pressure at normal body temperature parallel those recorded at 27-28 C, but are of a much lower order of magnitude. The average peak inspiratory pressure developed to move the tidal volume during normothermia was 24 cm H_2O, whereas at the reduced body temperature it was only 7 cm H_2O with the greatest imposed resistance. The effects of added resistance to tracheal flow on maximum air flow rates, inspiratory and expiratory, were also similar at normal and lowered body temperature. In the

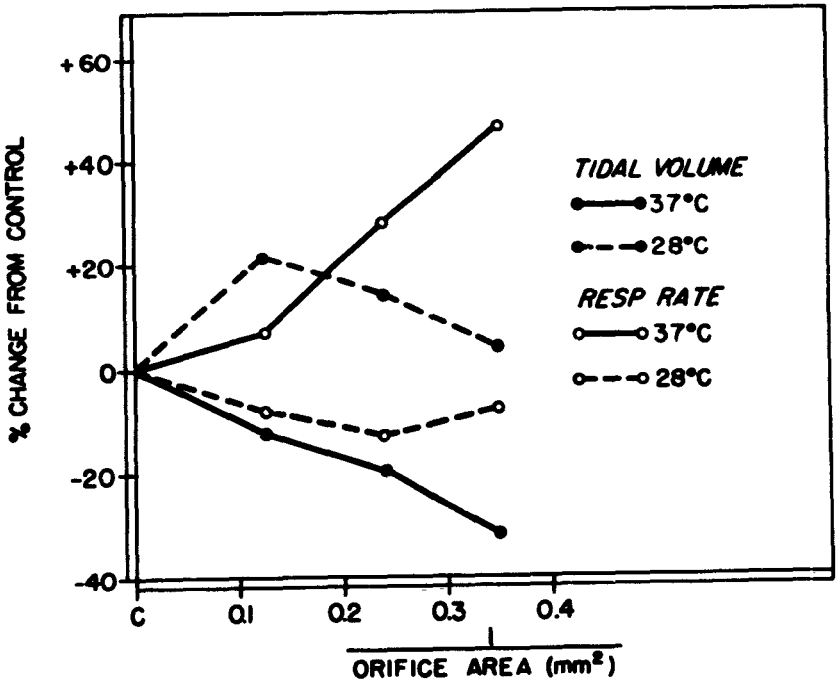


FIG. 6. Relative changes in respiratory rate and tidal volumes in response to increased airway resistance in normothermic and hypothermic dogs. Minimal resistance of respiratory apparatus is represented as control (C).

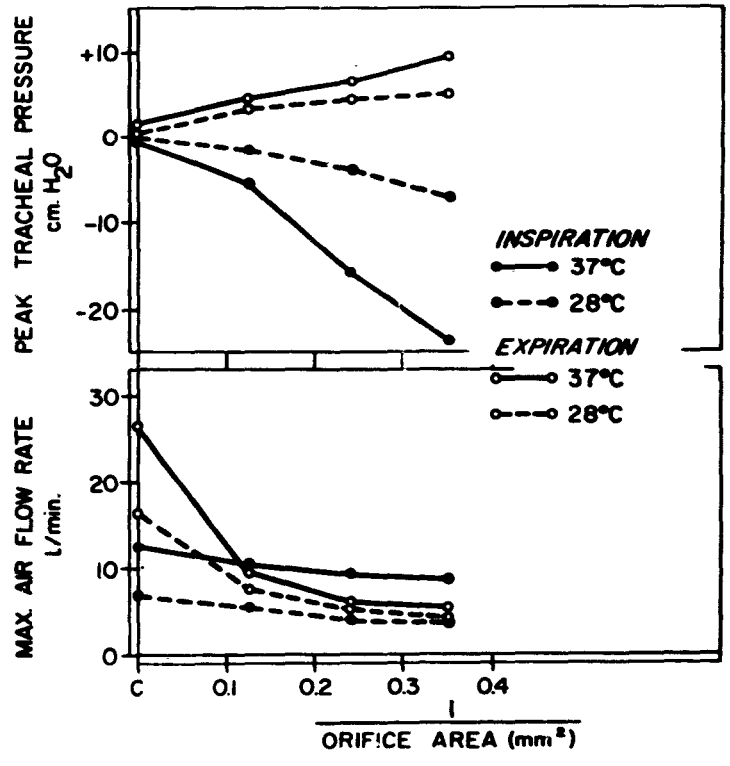


FIG. 7. Maximum tracheal pressures during inspiration and expiration and maximum inspiratory and expiratory flow rates in response to increased airway resistance in normothermic and hypothermic dogs. Minimal resistance of the respiratory apparatus is represented as control (C).

hypothermic condition the absolute values were lower but the relative changes in flow rates with a given resistance were approximately the same.

A most striking contrast of the influence of air flow impedance on breathing patterns is shown in Fig. 8. Whereas the duration of inspiration was altered in the same manner (percentage-wise), in response to resistances at both body temperatures a significant difference in duration of expiration was found. Expiratory time is progressively lengthened as airway resistance is increased at normal body temperature at the expense of the end-expiratory pause. As shown in Fig. 8, with the greatest impedance to flow used, time of expiration was increased 64%. In the hypothermic condition duration of expiration was doubled as a result of the greatest imposed resistance. The increased duration of expiration occurs here, as in normothermia at the expense of the end-expiratory pause. However, as was shown in Fig. 6, respiratory rate increased with the addition of airway resistance at normal body temperatures with complete obliteration of end-expiratory pause while at reduced body temperature there was still an end-expiratory pause due to two factors, namely, the slow respiratory rate which accompanies hypothermia and the further reduction in rate with added tracheal obstruction.

Oxygen consumption during minimal tracheal obstruction (control) was 5.0 ml/min/kg at 37 C and 2.6 ml/min/kg at 28 C, and increased progressively as the resistance to flow was increased. A rise of 20% in oxygen consumption (STPD) was recorded when both normothermic and hypothermic animals respired through the smallest orifice.

Cardiovascular responses. A significant difference in the responses of systolic pressure and heart rate to the imposed tracheal resistance in normothermic and hypothermic conditions is shown in Table 3. At normal body temperature systolic pressure increased progressively with an increase in resistance to air flow while heart rate progressively declined. Changes in heart rate probably reflect a reflex slowing of the heart in response to the elevated systolic pressure. Heart rate and systolic pressure were not altered in response to the impeded tracheal air flow in the hypothermic animals.

Cardiac output during various levels of tracheal obstruction at normothermic and hypothermic body temperatures is shown in Table 3. Although cardiac output was elevated in response to airway resistance at 37 C a significant difference from control occurred only during exposure to the smallest orifice. Tracheal obstruction did not significantly alter the cardiac output in the hypothermic condition (Table 3).

At normal body temperature alveolar ventilation was impaired as the magnitude of tracheal obstruction was increased. Arterial oxygen saturation decreased and end-tidal carbon dioxide concentration increased with increased obstruction to air flow (Table 4). Hypothermic animals responded to the imposed resistance without any significant fall in arterial oxygen saturation or rise in end-tidal carbon dioxide (Table 4), indicating no significant impairment of alveolar ventilation.

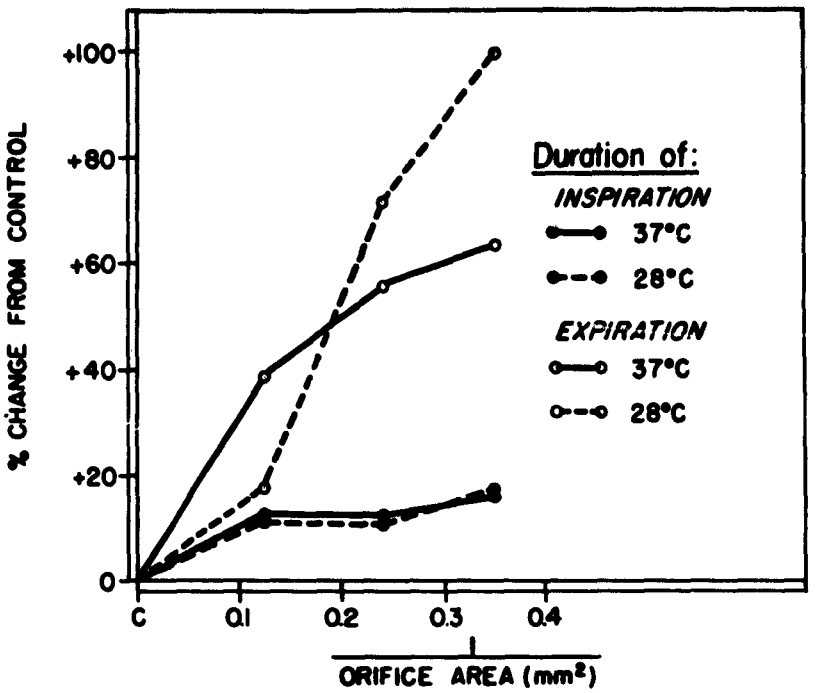


FIG. 8. Relative changes in duration of inspiration and of expiration in response to increased airway resistance in normothermic and hypothermic dogs. Minimal resistance of respiratory apparatus is represented as control (C).

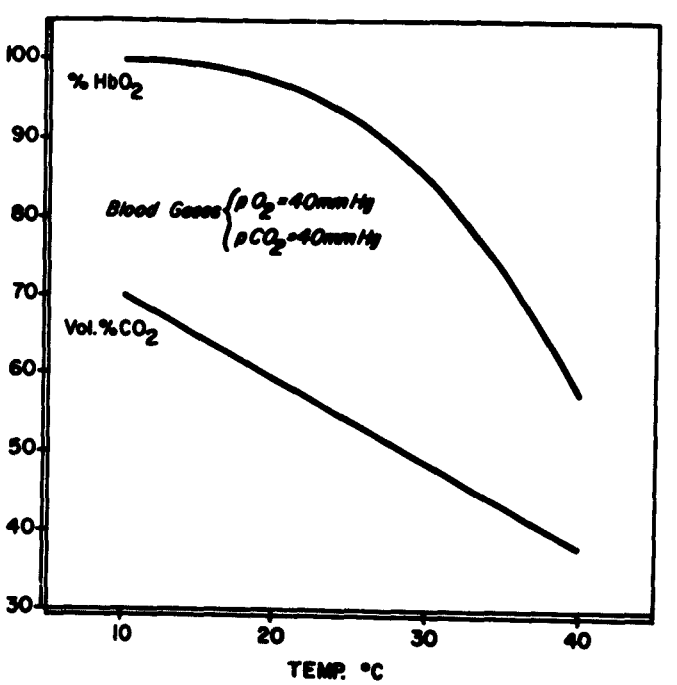


FIG. 9. Effect of temperature on gas equilibrium in blood of dogs.

TABLE 3. Cardiovascular responses to increased airway resistance during normothermia and hypothermia

Orifice Area, mm^2	Normothermia			Hypothermia		
	Systolic press., mm Hg	Heart rate, per min	Cardiac output, ml/min/kg	Systolic Press., mm Hg	Heart rate, per min	Cardiac output, ml/min/kg
Control	112	128	102	103	70	64
0.124	120	125	108	105	73	63
0.241	124	116	108	108	73	67
0.352	135	108	119	104	71	65

TABLE 4. Summary of 0_2 saturation of arterial and venous blood, end-tidal $C0_2$ tensions, and arterial $C0_2$ content values*

Orifice Area, mm^2	Normothermia				Hypothermia			
	%$Hb0_2$, arterial	%$Hb0_2$, venous	End-tidal $C0_2$, mm Hg	$C0_2$ content, art. vol. %	%$Hb0_2$, arterial	%$Hb0_2$, venous	End-tidal $C0_2$ mm Hg	$C0_2$ content, art. vol. %
Control	91.7	66.3	42.4	43.2	90.4	69.8	44.0	47.5
0.124	91.2	65.9	43.6	43.5	89.9	68.9	43.4	48.3
0.241	82.0	57.0	46.5	45.1	88.3	66.9	46.0	49.0
0.352	68.3	44.2	50.3	46.8	88.5	66.9	47.0	49.0

* Recorded in normothermic and hypothermic dogs in response to various levels of airway resistance.

The influence of temperature on the gas equilibrium in blood of dogs is shown in Fig. 9.

Samples of dog blood were equilibrated with a gas mixture containing carbon dioxide, oxygen, and nitrogen. Carbon dioxide and oxygen tensions were kept constant at 40 mm Hg, respectively. Equilibration was carried out at temperature ranging from 10-40 C by a method previously described (9). Blood samples were analyzed by Van Slyke manometric procedure (29) for simultaneous determination of oxygen and carbon dioxide. It will be observed that carbon dioxide content follows a linear relationship with temperature and full oxygen saturation of hemoglobin decreases in a curvilinear manner from 10 C to 40 C.

DISCUSSION

The results obtained in this investigation, relative to the effects of tracheal airway obstruction on respiratory responses in normothermic dogs are in agreement with those previously reported by Hall and Zechman (6). One of the significant findings in the present experiments concerns the influence of tracheal obstruction on the breathing frequency and tidal volume in hypothermic animals, as compared to normothermic animals. In the normothermic condition the prominent response to added airway impedance is a reduction in tidal volume and an increase in frequency of respiration, whereas in the hypothermic condition breathing rate decreased and tidal volumes increased. Hall and Zechman (6) reported a significant difference in the response of dogs breathing through an orifice having an area of 1.9 mm^2 while inhaling oxygen as contrasted to room air. There was a pronounced decrease in breathing rate while dogs were breathing 100% oxygen. Zechman, Hall, and Hull (30) found that increased air flow resistance in humans resulted in a decreased respiratory frequency. In these studies on human beings the level of resistance was not sufficient to produce hypoxia. Cain and Otis (4) have also reported a decrease in respiratory frequency in human subjects while breathing through imposed resistance. Hall and Zechman (6) postulated that the decreased frequency of respiratory activity in dogs breathing 100% oxygen indicated that increased air flow resistance, per se, decreases breathing rate, but if severe enough to cause hypoxia an increase in rate is initiated. Data reported in this presentation lend support to this theory since in normothermic animals there was an inverse relationship between breathing rate and arterial oxygen saturation. Increased resistance to flow resulted in a marked decrease in oxygen saturation and an increase in breathing rate. However, reduction of blood temperature to 28 C resulted in a slowing of the respiratory rate and an increase in tidal volume as a consequence of airway obstruction. Concomitantly arterial oxygen saturation did not change significantly, indicating that there was no impairment of alveolar ventilation. Although the oxygen dissociation curve shifts to the left as the blood temperature is reduced and hence loads at a lower arterial oxygen pressure the fact that there was no change in oxygen saturation as the magnitude of the obstruction was increased would indicate that in the hypothermic condition animals adjusted to the tracheal obstruction in such a manner that hypoxia did not develop.

It has been reported that positive pressure respiration produces a marked decrease in cardiac output and a fall in mean arterial pressure (12, 16). In the present experiments the obstruction to respiratory gas flow was present in both phases of the respiratory cycle and at normal body temperature the cardiac output increased and systolic pressure also increased. In the hypothermic condition there was no significant change in either cardiac output or systolic pressure. It seems that increase in cardiac output at normal body temperature is related to the large negative intratracheal pressure developed on inspiration, which aids venous return. On expiration the pattern of gas flow is such that positive intratracheal pressure is increased from that with no added resistance but is not increased to the same extent as the inspiratory pressures. In the hypothermic animals changes in peak tracheal inspiratory and expiratory pressures in response to obstruction are of the same order of magnitude, so that the effects of the increase in negative pressure are counteracted by the increase in positive pressure.

SECTION III

EFFECT OF HYPOTHERMIA ON REFLEX ACTIVITY IN THE ANESTHETIZED DOG

The extent of the pressor response to exogenously increased adrenalin seems to be critically dependent on the temperature of the recipient animal. Mukherjee et al. (20) reported that administration of adrenalin produced a much less rise of systemic blood pressure at 29°C as compared to pressor response evoked at prehypothermic temperatures. Pressor response was further diminished at 27°C. Koella et al. (15) also found that magnitude of the pressor response was dependent on temperature of the animal, but at 29.9°C they showed pressor response remained unchanged from that at 37°C. At 25°C it was as little as 1/5 of that produced by the same amount of adrenalin at 37°C.

To learn more about the influence of temperature on magnitude of pressor response to exogenously increased levels of epinephrine and nor-epinephrine the following experiments were performed at normal and at reduced body temperature (28°C). Circulatory and respiratory responses to hypoxic hypoxia and to bilateral carotid occlusion were also studied in the same animals at normothermic and hypothermic levels to assay the reflex activity of the hypothermic animal.

Methods. Eight mongrel dogs averaging 19.6 kg were used. Dial in Urethane (Ciba), 55 mg/kg i.p., was administered before surgical procedures and was not supplemented. Observations were made at blood temperatures of 37-38°C and repeated at 27-28°C. All observations were recorded during a steady state of body temperature.

Recordings. Respiratory variables were measured from gas flow patterns, as previously described (6). Recordings were made on a Miller oscillograph. Rectal and right heart blood temperatures were measured with copper-constantin thermocouples. Systemic arterial pressure was measured from a Statham pressure transducer connected to a catheter located in a femoral artery.

Epinephrine, 2 μg/kg, was injected into the superior vena cava from a catheter in an external jugular vein. Recordings were started prior to injection and continued until blood pressure returned to control level. Nor-epinephrine response was measured in the same manner. The common carotid arteries were clamped caudad to the carotid sinus for one minute during which time the pressor response had reached a steady state. Hypoxic hypoxia was induced by inhalation of 9% 0_2 in N_2 from a Douglas bag connected to the inspiratory side of a low resistance respiratory valve. Recordings were during the 5th minute of inhalation.

Following the observations at normal body temperature the animal was partially immersed in an ice water bath. At a blood temperature of 27-28°C the procedures used at 37° were repeated.

Results and discussion. Control values just prior to drug injection, carotid occlusion or hypoxic hypoxia, were used as unity and the various respiratory and circulatory responses to these conditions were expressed as percent changes from unity for both normothermic and hypothermic conditions (Table 5).

Responses to exogenously increased epinephrine and nor-epinephrine. Heart rate in the normothermic animals following injection of epinephrine was 125 as compared with a control level of 121 beats per minute. In the hypothermic animal heart rate fell from 73 to 59 beats per minute as a result of injection of epinephrine. However, in both hypothermic and normothermic animals, systolic and diastolic pressures were increased as a result of the epinephrine infusion. Systolic pressure was elevated approximately 10% more in hypothermic animals than in the normothermic condition. These results would indicate that hypothermia potentiates the response of systolic pressure to increased (exogenously) epinephrine at 28°C. This is especially noticeable when it is considered that the rise in systolic pressure in the hypothermic animal is greater than that in the normothermic animal even though heart rate is decreased in the hypothermic animal during blood pressure rise. Respiratory changes as a result of epinephrine injection were approximately the same under the 2 body temperatures studied. Respiratory rate was decreased from an average of 13.2 breaths per min to 11.0 in the hypothermic animals during the epinephrine-caused blood pressure rise. This is probably related to the interplay between blood pressure rise and respiratory rate changes usually seen as a result of the elevated pressure. End tidal CO_2 was increased from 5.7 to 6.1% in the normothermic animals and from 5.2 to 5.3% in the hypothermic animals following injection of epinephrine.

Quantitatively, 2 major differences were seen between responses to epinephrine and nor-epinephrine. Whereas little change occurred in heart rate in the normothermic animals following epinephrine injection the same dosage of nor-epinephrine decreased the average heart rate from 125 to 93 beats per minute. Approximately the same percentage decrease in heart rate was observed at reduced body temperature. Also, in the normothermic animals nor-epinephrine increased systolic pressure 64% but in the hypothermic state an increase 102% was seen. These increases were of a higher order of magnitude than were observed with epinephrine. Again (as with epinephrine) the greater increase of systolic pressure was observed in hypothermia in presence of a slower heart rate. These results indicate that the hypothermic animal is more sensitive to exogenously increased nor-epinephrine than is the normothermic animal.

TABLE 5. Percent Changes from Control of Circulatory and Respiratory Responses to Injections of Epinephrine and Nor-epinephrine, Bilateral Carotid Occlusion and Hypoxic Hypoxia in the Normothermic and Hypothermic Dog.

	Epinephrine		Nor-epinephrine		Carotid occlusion		Hypoxia	
	37°C	28°C	37°C	28°C	37°C	28°C	37°C	28°C
Heart rate	+ 3.3	-19.2	-25.6	- 23.6	+ 3.2	- 1.5	+ 11.4	+ 2.8
Syst. press.	+39.3	+49.5	+64.0	+101.9	+16.9	+ 8.9	+ 13.2	+ 6.3
Diast. "	+28.2	+25.7	+44.2	+ 87.5	+20.2	+11.9	+ 13.1	+16.9
Resp. rate	+ 2.2	-16.7	- 9.7	- 17.1	-10.9	-10.9	+120.0	+69.2
Tidal vol.	+ 7.0	+ 9.4	+ 9.8	+ 7.7	- 1.6	- 1.5	- 2.8	+12.4
Pulm. vent.	+ 9.3	+ .6	- 3.9	+ 6.1	-11.5	-11.2	+134.3	+95.9
Max. insp. flow	+22.9	+25.0	+ 2.6	+ 11.2	- 7.6	+ 2.0	+ 44.4	+27.2
" expir. "	+18.3	+17.8	+ .8	+ 3.8	+ 3.9	- 3.9	—	—
End tidal CO_2	+ 7.0	+ 1.9	+ 1.8	+ 3.8	0	+ 1.9	- 30.8	-16.1

The disagreement between the results of epinephrine administration reported here and those of Koella et al. (15) and Mukherjee et al. (20) may be related to depth of anesthesia and/or to dosage of the hormones administered. Doses of adrenaline administered by Mukherjee et al. varied from 100-200 µg in cats anesthetized (i.m.) with urethane in dosage of 1.5 to 1.8 g/kg. Koella and colleagues administered adrenalin at a dosage of 20 gamma but their animals (cats) were anesthetized with Dial urethane i.p., 25 mg/kg body weight, and immobilized with intocostrin so that artificial respiration was necessary. Our experiments are more closely related to those of Koella et al. with respect to dosage of adrenalin used but differ markedly in depth of anesthesia. However, we agree with these two groups on the findings that cardiac slowing induced by the pressor response is more marked in the hypothermic condition than in the normothermic.

Effect of hypothermia on carotid sinus reflex. Heart rate was essentially unchanged as a result of this maneuver at both normal and reduced body temperatures. Systolic pressure was increased from 130 to 152 mm Hg at normal body temperature and from 112 to 122 mm Hg at 27°C, increases of 17% and 9% respectively. Diastolic pressure was affected in essentially the same manner. Reduction in body temperature did not grossly change respiratory responses except for maximum inspiratory flow rate which decreased 7.6% in normothermia and increased 2% at 28°C as a result of carotid occlusion. These data show that the hypothermic animal retains reflex activity when body temperature is reduced 9-10°C. These findings are in agreement with Nashat and Neil (21) who elicited carotid sinus reflexes by raising the static pressure in one isolated carotid bifurcation. They found that respiratory and circulatory reflex responses were invariably present in cats at 26°C although the reflex fall of blood pressure produced by sinus hypertension was of less extent than at normal temperatures.

Effect of hypothermia on respiratory and cardiovascular responses to hypoxic hypoxia. Heart rate was increased 11% during the 5th min of exposure to the low oxygen gas mixture at normal body temperature: at reduced body temperature an increase of 3% was recorded. Systolic pressure increased 13.2% and diastolic pressure 13.1% at 37° as a result of the hypoxic hypoxia. These values were 6.3% and 16.9%, respectively at 28°C.

More pronounced differences between the warm and cold conditions occurred in respiratory responses to hypoxic hypoxia. Respiratory rate was more than doubled (37.6 to 82.7 breaths per min) during normothermia but increased only 69% (12.0 to 20.3) in hypothermia. Tidal volumes were relatively unchanged at the 2 levels of body temperature so that pulmonary minute volume was not as greatly elevated in hypothermia as at normal temperature. Maximum inspiratory air flow rates were different at the different body temperatures and are related to the changes in respiratory rates.

The normothermic animal hyperventilates relatively more than the hypothermic animal exposed to hypoxic hypoxia as evidenced by the differences in end tidal CO_2. Hypoxic hypoxia produced a decrease of 31% in end tidal CO_2 at normal body temperatures whereas a fall of 16% was recorded at the lowered body temperature. These results indicate that the hypothermic animal maintains the capacity to respond to hypoxic hypoxia via stimulation of the peripheral chemoreceptors.

Kilmore and Chase (14) reported the response of arterial pressure to inhalation of 15% O_2 was essentially the same under normothermic and hypothermic conditions in dogs. Systemic circulatory and respiratory responses of cats at 26°C to anoxia (produced by inhalation of 10% O_2 in N_2) were reported as very feeble by Nashat and Neil (21). The differences in results obtained by the various groups again may be attributed to depth of anesthesia or perhaps an inherent difference between hypothermic responses of cats and dogs.

SECTION IV

INFLUENCE OF VAGAL BLOCKADE ON RESPIRATORY AND CIRCULATORY FUNCTIONS IN HYPOTHERMIC DOGS

The literature relevant to the effects of hypothermia on physiologic functions is voluminous and has been extensively reviewed in recent reports (19, 17) but there still remains a paucity of data relative to the effectiveness of alveolar ventilation in spontaneously respiring animals during moderate reductions in body temperature. Severinghaus et al. (24, 25) have demonstrated an increase in anatomic and physiologic dead spaces in the anesthetized, artificially ventilated dog as a result of a reduction in body temperature to 25 C. The increased dead space was postulated to be the result of bronchodilation, indicating that the hypothermic animal has little or no vagal activity directed to bronchiolar musculature. Otis and Jude (23) found no real impediments to gas transport in the artificially ventilated hypothermic animal but there was a small increase in physiologic dead space. Although it was shown that dead-space volumes determined in a group of animals at normal body temperatures exhibiting spontaneous breathing were essentially the same as when these animals were artificially ventilated at the rate and depth of the spontaneous respiration (27), the same comparison was not made for hypothermic animals. Since hypothermic induction results in a respiratory pattern markedly different in rate and depth from that at normal body temperature it was thought of value to measure dead-space volumes in hypothermic animals exhibiting spontaneous breathing. Also, since it was previously shown (10) that vagal influences on the work of breathing are essentially the same at 28 C as at normal body temperature, indicating little or no loss of vagal afferent activity, the effects of vagal blockade on respiratory dead space have also been studied.

The ventilation-perfusion ratio obtained by dividing pulmonary ventilation by cardiac output was found to be curvilinearly related to body temperature by Kao and Schlig (13). Since it has subsequently been shown (23, 24, 25) that dead space is influenced by hypothermia, consideration was also given to the ventilation-perfusion ratios at normal and reduced body temperatures in this study.

METHODS

Twelve mongrel dogs, ranging from 16.3 to 26.7 kg in body weight (mean 20.3 kg), were used. Dial in urethan (Ciba), 55 mg/kg, was administered intraperitoneally and was not supplemented.

Respiratory measurements. Expired gas was collected in a plastic Douglas bag for periods of 6-10 min and subsequently measured in a

dry-gas meter. Respiratory rates were counted during the entire period of gas collection. Frequency of breathing was constant from minute to minute. Tidal volume was calculated from the volume of expired gas divided by the total number of breaths during the period of gas collection. Samples of gas were withdrawn for CO_2 analyses as the Douglas bags were being emptied through the gas meter. A Haldane gas analyzer was used to check the accuracy of the Liston-Becker CO_2 analyzer and was found to agree within .05%. In calculation of dead space the Liston-Becker analyses were used. End-tidal CO_2 was measured from the plateau of the expired CO_2 pattern recorded from a catheter attached to the tracheal cannula.

Anatomic dead space was calculated from the values for expired carbon dioxide content and alveolar carbon dioxide according to the Bohr formulation. Physiologic dead space was calculated from the Bohr equation by substituting arterial CO_2 for alveolar CO_2.

Cardiovascular measurements. Systemic arterial pressure was recorded from a Statham strain gauge attached to a catheter inserted through the femoral artery into the abdominal aorta. Cardiac output was measured by the dye dilution technique using cardio-green dye and a Waters X250 densitometer. Dye (.1 mg/kg) was rapidly injected through a catheter into the right ventricle, and blood was withdrawn from the femoral artery through the densitometer cuvette at 20 ml/min. The dye curves were replotted on semilogarithmic paper with extrapolation of the exponential decay in the usual manner. Calculation of cardiac output was by application of the Stewart-Hamilton formula (11).

Blood gas analysis. Eight to nine milliliters of blood in mercury-sealed syringes were drawn from the femoral artery just at the conclusion of oscillograph recordings. Blood samples were analyzed in duplicate for oxygen and carbon dioxide content by the combined gas manometric method of Van Slyke and Neill (29). The remainder of the blood was placed in a tonometer and equilibrated with gas mixtures of known composition by a method previously described (9). Equilibration was carried out at the temperature of the dog at the time blood was drawn. Gas mixtures which would give blood gas tensions in the estimated range of those in blood of the animal were used. Analyses of blood were carried out by the same procedure as for gas content. Results of these analyses were plotted on logarithmic graph paper, and from these dissociation curves the partial pressures of gas in the blood of the experimental animal were determined. Total oxygen capacity was determined by measuring total hemoglobin with an Evelyn colorimeter after conversion of hemoglobin to metcyanhemoglobin with Drabkin's reagent. The factor of 1.34 was used to calculate total oxygen capacity from the hemoglobin concentration value.

Vagal blockade. Functional bilateral vagotomy was accomplished by cooling the vagus nerves to 0.5-0.8 C by a method previously described (31). Briefly, it involves use of device whereby the nerve is placed in a silverlined groove of a hollow block through which water is circulated at rate of 4 liters/min. Warm water (38 C) was used for functional condition of vagi, and ice water was used to produce blockade.

Hypothermic induction. Body temperature, measured from thermocouples located in the rectum and in the inferior vena cava, was reduced to 28 C by immersing the animal in an ice-water bath. The animal's temperature was maintained at 28 C while the respiratory and circulatory measurements were made with vagi intact and vagi blocked. The animal was then warmed to 32 C by adjustments of the immersion bath, and the protocol used at 37 and 28 C was repeated. Ovservations were made on 12 animals; for each experiment the observations were made at the various temperatures on the same animal. Statistical analyses of the data were performed by using group-and paired-sample techniques. The null hypothesis was rejected at the 5% level of confidence.

RESULTS

The effects of vagal blockade on respiratory rate, tidal volume, and pulmonary ventilation at 37, 32, and 28 C (vena cava blood temperature) are shown in Table 6. Vagal blockade resulted in an increase in the amplitude and a decrease in the frequency of breathing at each of the temperatures studied. Pulmonary ventilation was not significantly changed when the vagi were cooled. As a result of vagal blockade respiratory rate decreased 25% at 37 C, 33% at 32 C, and 34% at 28 C and tidal volume increased 46% at 37 C, 35% at 32 C, and 37% at 28 C. These results indicate that the function of the vagus nerves in the Hering-Breuer reflex is essentially unchanged when body temperature is reduced.

Small and statistically insignificant increases in tidal volume were observed as the body temperature was lowered (Table 6). However, respiratory rates were significantly reduced with reduction in body temperature, with a concomitant reduction in pulmonary ventilation. The pulmonary ventilation at 28 C was one-third the volume at 37 C when the vagi were warm. Approximately the same relationships held when the vagi were cold.

Bilateral vagal blockade had no significant influence on heart rate, systolic and diastolic pressure, and cardiac output at the temperatures studied as shown in Fig. 10. Systemic arterial pressures at 32 C were not changed from those at 37 C; however, when the temperature was further reduced to 28 C both systolic and diastolic pressures were significantly less than these at 37 C. Heart rate decreased progressively as body temperature was lowered and at 28 C was reduced 43%. Cardiac output also declined with body temperature so that at 28 C it was also reduced by 43%.

TABLE 6. Influence of bilateral vagal blockade on respiratory parameters at normal and reduced body temperatures

	Vagi Warm	Vagi Blocked	Vagi Warm	Vagi Blocked	Vagi Warm	Vagi Blocked
Vena cava blood temp., C	37	37	32	32	28	28
Resp. rate, per min	28	21	19	12	9	5
Tidal vol., ml/min	217	316	237	320	249	342
Anat. dead space, ml	98	127	102	135	125	156
Physiol. dead space, ml	114	164	124	164	139	176
Pulm. vent. (BTPS), liters/ min	5.4	5.7	4.1	3.7	1.8	1.7
Alveolar vent. (BTPS), liters/ min	2.4	2.6	1.9	1.7	0.8	0.8
Hemoglobin sat., %	90	92	94	94	91	91
Alveolar PCO_2, mm Hg	38.3	35.8	34.2	33.1	40.6	41.1
Arterial PCO_2, mm Hg	47.1	44.9	43.0	42.0	49.0	48.3
a-A PCO_2, mm Hg	8.8	9.1	8.8	8.9	8.4	7.2
Alv. vent./C.O.*	1.1	1.2	1.2	1.2	0.6	0.6

Each value is average computed from observations on 12 anesthetized dogs. *Alveolar ventilation/cardiac output.

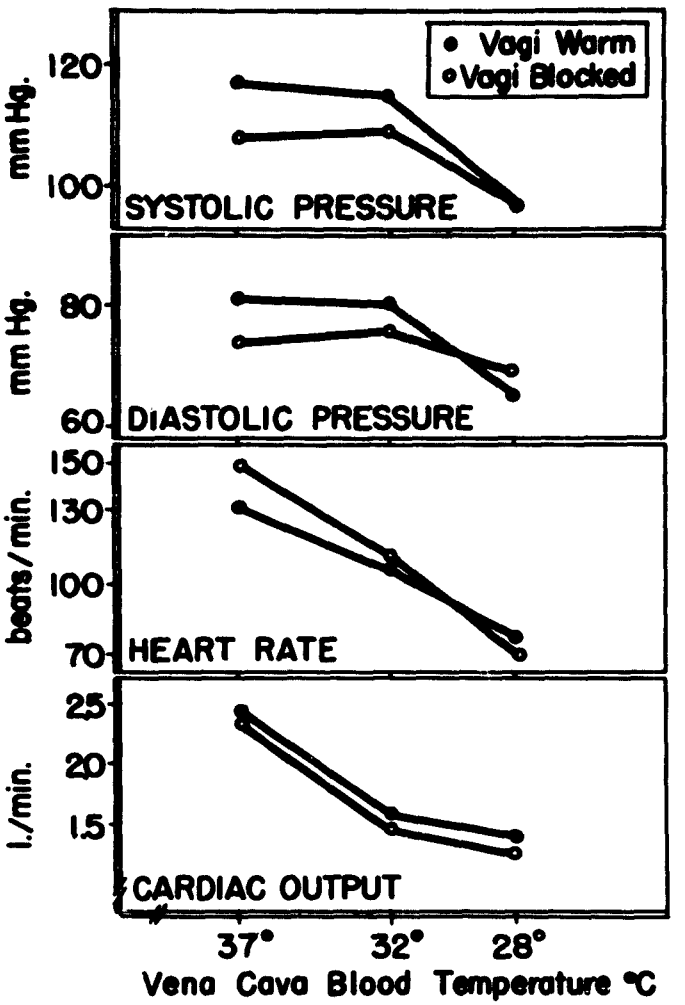


FIG. 10. Influence of vagal blockade at normal and reduced body temperatures on circulatory functions.

No significant changes from control (37 C) were observed in anatomic and physiologic dead spaces (Table 6) when the blood temperature was 32 C. However, at 28 C anatomic and physiologic dead spaces were 28% and 22% greater, respectively, than those at normal body temperature. Both at normal and at the reduced body temperatures, anatomic and physiologic dead spaces were significantly enlarged as a result of vagal blockade.

Alveolar ventilation, calculated from tidal volume minus physiologic dead space times respiratory rate, was increased 5% when the vagi were blocked at 37 C (Table 6). The increase was not statistically significant. No significant changes in alveolar ventilation were observed at 28 and 32 C as a result of vagal blockade as shown in Table 6. Alveolar ventilation at 28 C was approximately one-third as much as at 37 C.

The arterial-alveolar (end-tidal) carbon dioxide pressure differences (Table 6) were independent of body temperature and were not altered by vagal blockade. The a-A PCO_2 differences at 28 C were essentially the same as those at 32 and 37 C although both the end-tidal carbon dioxide and arterial carbon dioxide pressures at 32 C were significantly less than at 28 C. The reduction in carbon dioxide pressures at 32 C may be an experimental consequence of rewarming from 28 C. The relative hyperventilation, however, was not influenced by vagal blockade.

Ventilation-perfusion ratios obtained by dividing alveolar ventilation by cardiac output are shown in Table 6. Ventilation-perfusion ratios were independent of vagal blockade at normal as well as reduced body temperatures. No significant differences were observed in the calculated ratios at 32 and 37 C, which ranged from 1.09 to 1.20. However, at 28 C the ventilation-perfusion ratios were approximately one-half as large as those at 37 C.

DISCUSSION

The influence of vagal activity on the depth and amplitide of respiration was found to be as prominent in the hypothermic condition as during normothermia. This observation agrees with a previous report (10) in which it was found that at 28 C vagal blockade resulted in a decrease of 33% in respiratory rate and an increase in tidal volume. Alveolar ventilation decreased with reduction in body temperature. However, at normal and reduced body temperatures alveolar ventilation was not significantly altered by vagal blockade. This finding is contrary to that of Lim et al. (18), who reported an increase of 40% in alveolar ventilation as a result of bilateral vagotomy in normothermic animals. Simmons and Hemingway (28) also reported that vagotomy resulted in an increase in alveolar ventilation, as indicated by a fall in arterial carbon dioxide content. The discrepancy may reflect an experimental difference between blocking the nerves with cold and actual nerve section.

Vagal blockade resulted in significant increases in anatomic dead space at normal and reduced body temperatures. No significant changes in anatomic dead space were observed when body temperature was reduced 5 C below normal. Further reduction of body temperature to 28 C caused anatomic dead space to be significantly greather than that at 37 C. These findings on spontaneously respiring dogs are in agreement with the work of Severinghaus and collaborators (24, 25) on artificially ventilated dogs at a temperature of approximately 25 C. The increased anatomic dead space was postulated to be a consequence of bronchodilation as the result of a decrease in vagal activity at 25 C. That this is possible cannot be denied with the data presented here. However, vagal activity in regard to bronchiolar musculature must still be substantially present at 28 C since vagal blockade at 28 C resulted in a further significant increase in anatomic dead space (Table 6). This differs from the reports of Severinghaus et al. (24, 25) that vagotomy increased dead space as much as cooling the animal to 25 C.

Physiologic dead space was also significantly increased as a result of vagal blockade at normal and reduced body temperatures. Changes in functional residual capacity are known to be related to changes in anatomic and physiologic dead space, although it has been reported that functional residual capacity is not changed by hypothermic induction (3, 24).

The hypothermic dog, breathing spontaneously, characteristically exhibits a respiratory pattern that is markedly different from the normothermic animal. The respiratory rate is reduced with a small increase in tidal volume. The reduction in rate is usually seen as a prolongation of the end-expiratory pause and a lengthening of the duration of the expiratory phase of the respiratory cycle. The inspiratory phase of the cycle is only slightly altered when considered as a percentage of the duration of the complete cycle. As a result of the decreased rate of breathing and an increase in respiratory dead space, alveolar ventilation at 28 C was approximately one-third that at 37 C. Nonetheless, arterial hemoglobin oxygen saturation was not significantly different from that at 37 C and arterial carbon dioxide pressure was also unchanged. These values indicate that even though the volume of alveolar ventilation is reduced, it is being regulated to satisfy the metabolic requirements at 28 C.

The failure to cause significant changes in heart rate and systemic pressures by vagal blockade in normothermic animals is consistent with a previous report from this laboratory (31). It seems justified to state that the anesthetized dog has little or no vagal tone with respect to cardiac activity. Reduction of heart rate and systemic

pressures coincident with reduction of body temperature agrees with findings of many other workers using hypothermia. Cardiac output at 28 C was approximately 55% of that at 37 C, which represents a fall of 5% per degree fall in temperature and agrees with previous reports. The ratios of alveolar ventilation to cardiac output (ventilation-perfusion ratio) at 37, 28, and 32 C showed no effects from vagal blockade. Ventilation-perfusion ratios at 32 C were not significantly different from those at 37 C, indicating that both ventilation and cardiac output are equally decreased, but at 28 C the ventilation-perfusion ratios were significantly less than at 32 or 37 C. These findings suggest that the reduction in cardiac output at 28 C is not as great as the reduction in ventilation, and indeed if alveolar ventilation is adequate as judged by the blood gases (0_2 and $C0_2$) then cardiac output is almost twice that needed to adequately perfuse the lungs. Kao and Schlig (13) showed that during hypothermia cardiac output decreases but that blood flow in relation to metabolic demand increases. The ventilation-perfusion ratios agree with their finding.

The a-A $PC0_2$ differences were not significantly altered by reduction of body temperature. These observations on spontaneously respiring dogs are essentially the same as those found by Severinghaus et al. (25) for artificially ventilated animals at approximately 25 C. Otis and Jude (23) also found no change in the a-A $PC0_2$ differences at various levels of hypothermia in artificially ventilated dogs. Therefore, the data presented here for spontaneously respiring dogs substantiate the findings of Severinghaus et al. (25) and Otis and Jude (23), in artificially ventilated dogs, that there is no impairment of gas transport and gas exchange in the hypothermic dog.

SECTION V

EFFECT OF HYPOTHERMIA ON VENTILATORY RESPONSE TO CARBON DIOXIDE INHALATION AND CARBON DIOXIDE INFUSION IN DOGS

It is readily observed that animals in the hypothermic state exhibit a marked reduction in spontaneous respiratory activity. Osborn (22) showed that dogs subjected to hypothermia undergo considerable changes in arterial pH. Initial alkalosis associated with hyperventilation was followed by acidosis attributed to carbon dioxide retention. Osborn found that retention of carbon dioxide was not entirely respiratory since it was not prevented by artificial respiration at normal minute volumes. Severinghaus et al. (25) reported that the differences between arterial and end-expiratory carbon dioxide tensions were not altered or even reduced during hypothermia, thus suggesting no impairment in carbon dioxide excretion. Cranston et al. (5) reported a fall in arterial blood pH with decreasing temperature in anesthetized dogs in which hypothermia was induced by blood stream cooling. The fall in pH was associated with a rise in carbon dioxide content and a concomitant increase in arterial carbon dioxide tension. The ratio of pulmonary ventilation during inhalation of 6% carbon dioxide in air over the pulmonary ventilation during inhalation of room air during normal rectal temperatures was not statistically different from the same ratio during hypothermia. Interpretation of data collected by Cranston et al. is difficult because their animals were given repeatedly intermittent injections of small doses of anesthetic. This procedure made it difficult to ascertain if the depth of anesthesia was the same before and after cooling.

The present investigation was undertaken in an attempt to learn more about respiratory regulation and carbon dioxide elimination in the hypothermic state. The problem was attacked in two ways. In one series of experiments, animals were made to inhale two gas mixtures of CO_2 in air (3 99% CO_2 in air and 5.52% CO_2 in air by Haldane analysis) before, during and after hypothermia. Various respiratory and circulatory parameters were studied. In another series gaseous CO_2 was infused into the hypothermic animal and expired gas was analyzed for CO_2 content to determine if a CO_2 elimination problem existed.

METHODS

Carbon dioxide—air gas mixture inhalation. In this phase of the experiment eight dogs, 12.7-19.6 kg (mean 17.1 kg) in weight, were used. Following administration of Dial (55 mg/kg i.p.), hair was shaved from the chest and hind limbs and the animal was placed on a specially constructed V-shaped aluminum trough. A thermocouple was inserted into the rectum to a depth of 10 cm, a second thermocouple was inserted

into the lower 2/3 of the esophagus and a third was inserted into a femoral vein and placed into the inferior vena cava. The emf generated by rectal and blood thermocouples was measured on a Leeds-Northrup type K2 potentiometer and converted to degrees centigrade by appropriate conversion tables. The esophageal temperature was recorded directly from a Yellow Springs Instrument Company Tele-thermometer. A previously described (6), specially constructed tracheal cannula was inserted. A low resistance respiratory valve was attached to the tracheal cannula so that the animal inspired the carbon dioxide air gas mixture from a 100-liter plastic Douglas bag, the expired gas was directed through a gas meter. A wire cloth flow-meter was inserted in the inspiratory path for recording the pattern of inspiration. End-tidal $C0_2$ was measured with a Liston-Becker $C0_2$ analyzer immediately following the gas volume measurement. All recordings were made on a Miller oscillograph. Arterial blood pressure was recorded from a Statham pressure transducer to which a polyethylene catheter had been attached and inserted through a femoral artery to the abdominal aorta. Blood samples were collected in heparinized syringes from a pet cock attached to the femoral artery catheter.

Blood samples were analyzed for oxygen content, oxygen capacity and carbon dioxide content with a Van Slyke manometric gas analyzer (29). Blood samples were equilibrated tonometrically at the temperature at which the sample was withdrawn. Arterial $PC0_2$ values were calculated from $C0_2$ content at various partial pressure of $C0_2$. Total hemoglobin was determined by converting hemoglobin in the samples to metcyanhemoglobin and reading the concentration on an Evelyn photo-electric colorimeter. The factor of 1.35 was used to calculate total hemoglobin oxygen capacity.

Each experiment was conducted as follows: observations were recorded with the animal maintaining a normal rectal temperature and breathing room air. The animal was then connected to the 4.0% $C0_2$-air mixture to inhale until a relatively steady state was reached as indicated by the volume of expired gas which was recorded at the end of each minute. All observations were of an 8-10 minutes duration. Oscillograph recordings were made during 1st, 3rd, 5th and 8th or last minute of the gas inhalation. Immediately thereafter, the animal was given the 5.5% $C0_2$-air mixture to inhale and the same procedure was used with respect to recordings. All data reported are those collected during the steady state of each gas-mixture inhalation. Blood samples were collected at the end of each period of gas inhalation.

After observations at normal body temperature were made, the animal inspired room air and the animal board was lowered into a large metal tank. The tank contained an ice-water mixture in which the animal was immersed in the supine position to a depth just below the level of the tracheal cannula. Ice water was continuously poured over the thoracic and abdominal areas. The animal was cooled to a rectal temperature of 29°C in 30-40 minutes. At a rectal temperature of 29°C the ice water was drained from the tank and rectal temperature fell very

slowly, usually stabilizing at 27°-28°C. When a stable rectal temperature was reached, observations were made while the animal inhaled room air, 4.0% CO_2-air and 5.5%CO_2-air, respectively, until a steady state was recorded for each condition. Blood samples were drawn as before.

Following observations in the hypothermic condition, hot water (42-45°C) was added to the tank to the same depth, and water was poured over the thoracic and abdominal areas. Rewarming to the prehypothermic rectal temperature was accomplished in 60-75 minutes. Respiratory and circulatory measurements were made with the various gas mixtures following the same protocol used during normothermia and hypothermia.

Carbon dioxide infusion. This series of experiments was performed to investigate ability of the hypothermic animal to respond to a carbon dioxide stress. Five dogs of 14.5 kg to 18.6 kg (mean 16.3 kg) body weight were used. Dial in urethane (55 mg/kg i.p.) was used as in the previous series. The tracheal cannula was inserted and the low-resistance respiratory valve attached to the cannula. A wire screen flowmeter was attached to the inspiratory side of the valve. An atmosphere of oxygen was also provided on the inspiratory side and all observations were made while the animal was inhaling 100% O_2 at atmospheric pressure. Expired gas was collected in a 100-liter-capacity plastic Douglas bag. The bag was emptied through a dry gas meter and a sample of gas was withdrawn from a side arm on the gas meter for an analysis of the CO_2 concentration of the mixed, expired gas. Carbon dioxide analyses were made on a Haldane gas analyzer. Respiratory rate, maximum inspiratory flow rate and tidal volume were calculated from inspiratory flow patterns recorded from the screen flowmeter. Arterial blood pressure was recorded from a polyethylene catheter inserted through the femoral artery to the abdominal aorta. Measurement was from a Statham pressure transducer. Blood samples were withdrawn from this catheter at the end of observations made in the normothermic state and at the end of observations made in the hypothermic state before and after the infusion of gaseous carbon dioxide.

Carbon dioxide was infused through a large bore polyethylene catheter inserted through a femoral vein to a point near or into the vena cava. The gas was infused from a high-pressure cylinder of carbon dioxide (99.8% CO_2 by analysis) through a wet gas meter at the average rate of 67 ml (BTPS) per minute for 20 minutes.

A comparison of the volume of carbon dioxide expired during periods of observations (20 minutes) in the normothermic condition and in the hypothermic condition before and after the gas infusion was made. In some cases carbon dioxide was infused during normothermia to check

the response against that observed in other studies (7, 8). In still other cases, expired gas was collected and the CO_2 volume was calculated during a 10-minute period following gas infusion during hypothermia.

RESULTS AND DISCUSSION

Carbon dioxide inhalation series. The average respiratory and circulatory responses to inhalation of room air, a 4.0% CO_2-air mixture and a 5.5% CO_2-air mixture are presented in table 7. The results as shown are from eight dogs exhibiting unaided spontaneous respiration during periods of normothermia, hypothermia and again during normothermia after hypothermia. These values are averages of those which were recorded during the steady state, reached in 8-10 minutes for each dog.

Normothermia. During normothermia an increase in carbon dioxide content of the inspired air caused a slight increase in respiratory rate and a more pronounced increase in tidal volume. Concomitantly there was an increase in pulmonary ventilation. The increase in respiratory rate resulted from the shortening of the duration of inspiration while tidal volume was increased by increasing the maximum inspiratory flow rate from 18.9 l/min. during room-air inhalation to 27.9 l/min. during inhalation of 5.5% CO_2 in air when the rectal temperature was 37°C. End-tidal CO_2 (alveolar) showed a progressive increase as the inspired CO_2 tension was increased. Heart rate was 12% lower during inhalation of 5.5% CO_2 in air than during room-air inhalation. Systolic and diastolic pressure were relatively unaffected by changing the CO_2 content of the inspired gas. While the volume of CO_2/100 ml of blood was not altered significantly, arterial PCO_2 increased as the tension of the inhaled CO_2 was increased.

Hypothermia. Respiratory rate, tidal volume and minute volume were all decreased from the normothermic levels during spontaneous respiration in the hypothermic state. These responses were markedly reduced regardless of which gas was inspired. The duration of inspiration was prolonged and maximum inspiratory flow rates were greatly reduced when compared with maximum flow rates observed during normothermia. End-tidal CO_2 did not vary much from the normothermic levels. Heart rate systolic blood pressure and diastolic blood pressure were depressed during hypothermia, but the decreases did not show any dependency on the inspired gas composition. Hypothermia generally evoked an increase in hemoglobin concentration but the hemoglobin-oxygen saturation exhibited a decrease. There was an increase in carbon dioxide content per 100 ml of blood due to the simple physical condition of lowered blood temperature. Carbon dioxide content in blood was dependent on the tension of the carbon dioxide in the inspired gas,

TABLE 7. Average Respiratory and Circulatory Responses to Inhalation of Various Gas Mixtures Before, During and After Water Immersion Hypothermia

	Normothermia			Hypothermia			Animal Rewarmed to Normothermia		
	Room air	4.0% CO_2	5.5% CO_2	Room air	4.0% CO_2	5.5% CO_2	Room air	4.0% CO_2	5.5% CO_2
Resp. rate/min.	22	25	32	12	11	12	26	32	35
Puim. vent., l/min. (BTPS)	3.60	5.08	7.31	1.33	1.51	1.77	4.21	5.00	9.64
Duration of insp., sec.	1.33	0.98	0.83	2.36	2.42	2.24	0.85	0.86	0.82
Max. insp. flow, l/min.	17.9	22.0	27.9	7.4	8.1	8.4	20.6	26.6	29.0
End-tidal CO_2, %	5.4	6.5	7.3	5.1	6.4	7.6	4.9	5.8	6.5
Heart rate/min.	159	152	140	75	69	69	169	161	154
Systolic press., mm Hg	150	148	149	125	126	125	166	161	158
Diastolic press., mm Hg	106	105	101	86	83	80	113	107	102
Hemoglobin, gm/100 ml	15.2	15.7	15.5	16.7	16.7	16.9	16.3	16.5	16.3
% HbO_2 (art.)	90	92	91	81	81	79	89	92	93
CO_2 vol., % (art.)	38.9	41.1	41.4	44.9	47.6	49.0	35.8	37.8	39.9
PCO_2, mm Hg (art.)	45	53	55	42	47	52	40	46	51

increasing progressively with the increase in inspired carbon dioxide tension. Arterial carbon dioxide tensions were lower during hypothermia as a result of the increased capacity of blood for carbon dioxide at the lower blood temperature. However, arterial carbon dioxide tension did increase as the inspired carbon dioxide tension was increased.

Animal rewarmed to normothermia. In general all parameters measured returned to the prehypothermic level. Some values tended to overshoot and others undershoot; but responses to increasing the CO_2 tension in the inspired gas were qualitatively essentially the same.

Pulmonary ventilation was depressed to various degrees during hypothermia, table 7, with some correlation between the degree of depression and the tension of CO_2 in the inspired gas. Inspiration of room air during hypothermia resulted in a pulmonary ventilation which was 63% lower than during normothermia. The same comparison for 4.0% CO_2-air mixture revealed a ventilation that was 70% lower and for 5.5% CO_2-air it was 75% lower. However, when data are compared in a manner which compensates for the depression of spontaneous respiration during hypothermia, a different scheme is found. Figures 11 and 12 were constructed from the average ratio of the various respiratory parameters measured under changes in body temperature. Further, the data are ratios of the response of the animals to increased CO_2 tension of the inspired air using the response to room-air inhalation as unity. An added advantage of this method is that each animal acts as his own control. On the basis of these calculations it was found that inhalation of the 4.0% CO_2-air mixture produced an increase of 39% in pulmonary ventilation during normothermia (fig. 11); during hypothermia the same gas mixture increased pulmonary ventilation 13% over room-air inhalation. Ratios of respiratory rate, maximum inspiratory flow rate and end-tidal CO_2 are also shown in figure 11. The ratios of 5.5% CO_2 to room-air inhalation for respiratory rate, maximum inspiratory flow rate, end-tidal CO_2 and pulmonary ventilation are shown in figure 12. This gas mixture increased pulmonary ventilation by 94% during normothermia and 34% during hypothermia.

Cranston et al. (5) reported a mean increase in respiratory minute volume of 51.3% when animals respired 6% CO_2 in air at a rectal temperature of 36.5°—38.5° C. Reduction of rectal temperature to 25°—27° C resulted in a mean increase in respiratory minute volume of 43.5%. These values were not statistically different. Hence, their animals seem to have exhibited a more pronounced response to the increased CO_2 in the inspired gas during hypothermia than those reported here. These differences may well be a reflection of the anesthetic procedures used. Some of their animals showed a greater response to the gas mixture during hypothermia than during

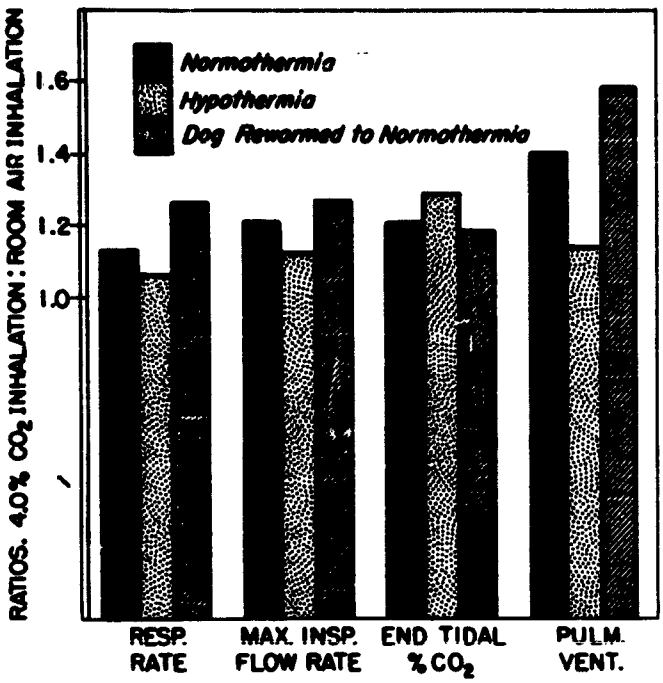


FIG. 11. Effect of inhalation of 4.0% CO_2 in air on respiratory regulation during hypothermic stress. Unity (1.0) represents the level of respiratory responses of animals inspiring room air at normal and reduced body temperatures.

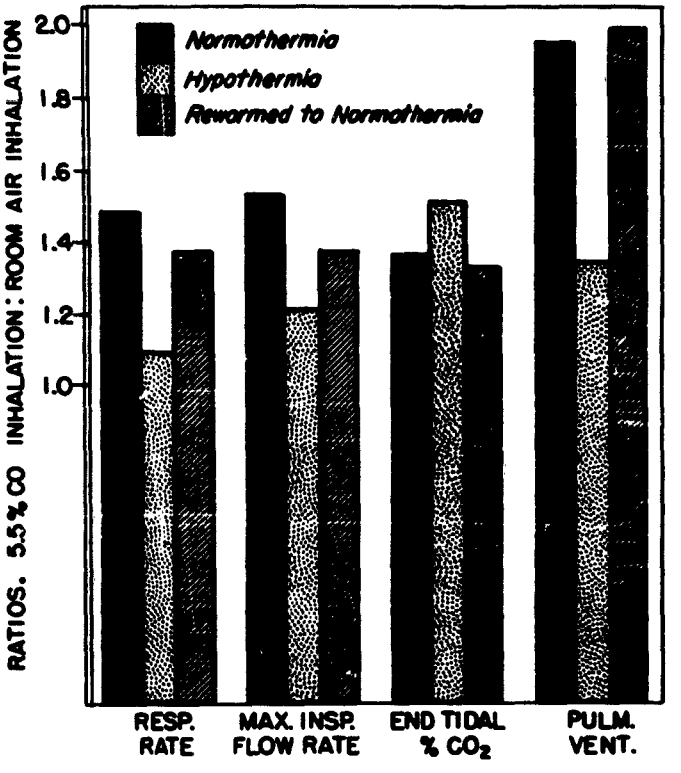


FIG. 12. Effect of inhalation of 5.5% $C0_2$ in air on respiratory regulation during hypothermic stress. Unity as in fig. 11.

normothermia. None of the animals in our series showed this.

Severinghaus (26) has criticized the data of Cranston et al. (5) for two reasons: "(1) The response of the control dogs to CO_2 at 37° was only 1/3 of the 'normal' expected response. (2) The response at 25-27°C was given as a percentage of the already doubly depressed ventilation at that temperature." Our data tend to support the first statement in so far as the pulmonary ventilation of our animals was almost doubled as a result of breathing 5.5% CO_2 in air at normal body temperatures while Cranston et al. (5) showed only a 50% increase. The second point is more difficult to reconcile. It seems that if spontaneous respiration is depressed as a result of low temperature, it would only be valid to use the ventilation observed during inhalation of room air in the depressed state of hypothermia as the basis for determining if there is any ventilatory response to increased CO_2 tension of the inspired gas. On this basis it can be concluded that the animal does exhibit a sensitivity to increased CO_2 tension during the hypothermic state. On the other hand if one does not accept the comparison as valid, then it must be concluded that the hypothermic animal does not respond to increased CO_2 tension.

CO_2 infusion. In order to further test the response of the hypothermic animal to CO_2 stress, gaseous CO_2 was infused into the animal. In previous studies (7, 8) it was found that the normothermic animal tolerates infusion of CO_2 and responds by increasing pulmonary ventilation. The ventilation reaches a steady state during the infusion at which time the volume of CO_2 expired is almost equal to that being infused plus that which was expired just prior to the infusion. Data collected from five dogs are presented in table 8. It was found that the hypothermic animal responds to CO_2 infusion by increasing pulmonary ventilation although to a lesser extent than the normothermic animal (7, 8). Table 9 is a presentation of the data relative to the volume of CO_2 expired by the normothermic animal, and by the hypothermic animal before and during CO_2 infusion. These data show that the hypothermic animal is capable of responding to CO_2 stress by increasing pulmonary ventilation to the extent that the amount of CO_2 expired is greater than that infused. It is, however, not equal to that infused (1.34 liters, BTPS), plus that expired prior to the infusion (0.79 liters). Differences were expected for two reasons: 1) the increased blood capacity for CO_2 at the low temperature and 2) the animals' expired volumes of CO_2 which were larger than the preinfusion volumes after the infusion stopped.

In three animals expired gas was collected and analyzed for CO_2 content for 10 minutes following gaseous CO_2 infusion in the hypothermic state. In each case it was found that the animal continued to expire CO_2 in excess of the preinfusion level.

TABLE 8. Average Respiratory and Circulatory Responses of Five Dogs During Normothermia, Hypothermia and CO_2 Infusion of 67 Ml (BTPS) CO_2 Per Minute for 20 Minutes

	Normothermia	Hypothermia*	CO_2 Infusion During Hypothermia
Resp. rate/min.	14.4	9.9	17.2
Tidal vol., ml. (BTPS)	176	155	179
Pulm. vent., l/min. (BTPS)	2.4	1.6	3.3
Duration insp., sec.	1.3	2.8	1.8
Max insp. flow, l/min.	14.0	7.8	13.8
Heart rate/min.	154	84	63
Systolic press., mm Hg	120	110	100
Diastolic press., mm Hg	90	82	68
Hemoglobin, gm/100 ml	14.5	15.4	17.2
% HbO_2 (art.)	100	100	96
CO_2 vol., % (art.)	41.1	44.3	54.1
PCO_2, mm Hg (art.)	45	40	64

TABLE 9. Comparison of Volumes of CO_2 Contained in Expired Gas During Normothermia, Hypothermia (28°C), and During a 20-Minute Period of CO_2 Infusion During Hypothermia

	Normothermia	Hypothermia	CO_2 Infusion During Hypothermia
Liters of gas expired (BTPS)	48.0	33.39	58.14
Per cent CO_2 in expired gas	2.97	2.57	2.65
Vol. CO_2 expired (BTPS)	1.40	0.79	1.42
Vol. CO_2 infused (BTPS)			1.34

Blood gas data during normothermia and in hypothermia before and after CO_2 infusion are presented in table 8. The blood carbon dioxide content was greater in the hypothermic animal preinfusion than in the normothermic animal while the CO_2 tension of the hypothermic animal was less than in the normothermic animal. These data are qualitatively the same as those determined in the normothermic and hypothermic animals inspiring room air, table 7. During CO_2 infusion the volume of CO_2/100 ml blood was increased from 44.3 vol. % to 54.1 vol. % while the arterial tension rose from 41.4 mm Hg to 65.0 mm Hg.

Data collected during the inhalation of increased CO_2 and that during the infusion of CO_2 seem to support the findings of Cranston et al. (5) in that the hypothermic animal does exhibit a sensitivity to CO_2 tension but not necessarily of the same order of magnitude as does the normothermic animal.

SUMMARY

Hypoxia and body temperature operate reciprocally in determining the utilization of oxygen of rats in a closed environment. Body temperature during hypoxia can be maintained at normal levels when environmental temperatures are between 32° C. and 33° C. Critical oxygen tensions of rats in a closed microenvironment are influenced by body temperatures. Lower body temperatures permit lower critical oxygen tensions. Acclimatization to hypoxia has little effect upon minimal critical oxygen tension and any significant affect is adverse. Hemoglobin affinity for oxygen appears to be more important than the quantity of hemoglobin present.

Respiratory and circulatory responses to three levels of imposed tracheal obstruction were measured in normothermic dogs; the same measurements were repeated after the blood temperature of the animals had been reduced to 28° C. by immersion in ice water. Respiratory rate increased, tidal volume decreased, and arterial oxygen saturation progressively declined as a result of tracheal impedance at 37° C. The induction of the hypothermic condition caused a fall in respiratory rate, an increase in tidal volume, and no change in arterial oxygen saturation in response to the same obstruction to air flow. Cardiac output and systemic pressure increased as the magnitude of obstruction was increased in the normothermic animals but were not altered by the same degree of obstruction in the hypothermic animals. The differences in responses observed at the two temperatures studied seem to be related to the degree to which hypoxia develops in the normothermic animals as a result of tracheal air flow impedance.

Evidence is presented which indicates that pressor response to injections of epinephrine and nor-ephinephrine is potentiated in the anesthetized dog at blood temperatures of 27 - 28° C. The augmented response to nor-epinephrine was greater than that for epinephrine. Evaluation of respiratory and circulatory responses to bilateral carotid occlusion and hypoxic hypoxia indicates that the hypothermic dog retains reflex activity but magnitude of the responses is less than that at normal body temperature.

Anatomical and physiological dead spaces were enlarged as a result of reduction in body temperature to 28° C. in spontaneously respiring anesthetized dogs. Respiratory dead space at 32° C. was not significantly different from that at normal body temperature. Vagal blockage resulted in an increase in tidal volume and decrease in respiratory frequency and increased anatomic and physiologic dead space at normal and reduced temperatures. Alveolar ventilation and cardiac output declined equally (percentage-wise) with reduction in body temperature to 32° C.; at 28° C. alveolar ventilation fell more precipitously so that alveolar ventilation-cardiac output ratio (ventilation-perfusion) at 28° C. was approximately one-half that at 37° and 32° C. Arterial-alveolar carbon dioxide pressure

differences were independent of temperature and vagal blockage. The results indicate no impairment of gas transport or gas exchange at 32° or 28° C. in spontaneously respiring anesthetized dogs.

Some respiratory and circulatory responses to carbon dioxide stress during ice-water immersion hypothermia were studied in 13 dogs. Stresses were imposed by increasing the carbon dioxide tension of the inspired gas in eight animals and by intravenous infusion of gaseous carbon dioxide in five other animals. It was found that when compensation is made for the depressed ventilation exhibited at low body temperature, animals responded to the carbon dioxide stresses in essentially the same manner in the hypothermic as in the normothermic state. However, the responses are of a lower order of magnitude.

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Unclassified report

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